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Original Article

Clinical utility of mid-arm muscle circumference cut-offs for detecting protein-energy wasting in Malaysian hemodialysis patients

Qian-Qian Hoong [a], Jun-Hao Lim [a], Lee-Fang Teong [b], Nurul Iman Hafizah Adanan [a], Ban-Hock Khor [c], Sharmela Sahathevan [d], Pramod Khosla [e], Tilakavati Karupaiah [f,g], Zulfitri Azuan Mat Daud [a,h,i,*]

[a] Department of Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, UPM Serdang 43400, Selangor, Malaysia
[b] Department of Dietetics and Foodservice, Hospital Selayang, Lebuhraya Selayang - Kepong, Batu Caves 68100, Selangor, Malaysia
[c] Faculty of Food Science and Nutrition, Universiti Malaysia Sabah, Kota Kinabalu 88400, Malaysia
[d] Department of Nutrition, Dietetics and Food Science, IMU University, Bukit Jalil 57000, Kuala Lumpur, Malaysia
[e] Department of Nutrition and Food Science, Wayne State University, Detroit, MI 48202-0340, United States
[f] School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya 47500, Selangor, Malaysia
[g] Food Security & Nutrition Impact Lab, Taylor's University, Subang Jaya 47500, Selangor, Malaysia
[h] Research Centre of Excellent on Nutrition and Non-Communicable Diseases (RCoE-NNCD), Universiti Putra Malaysia, UPM Serdang 43400, Selangor, Malaysia
[i] Department of Dietetics, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, UPM Serdang 43400, Selangor, Malaysia

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SUMMARY

Objective: Protein energy wasting (PEW) is a severe form of malnutrition prevalent among hemodialysis (HD) patients. A key diagnostic criterion outlined by the International Society of Renal Nutrition and Metabolism (ISRNM) for PEW is a reduction in mid-arm muscle circumference (MAMC) below the 50th percentile (P_{50}) of the reference population by more than 10%. However, the absence of population-specific MAMC cut-offs makes diagnosing PEW challenging. This study aimed to establish, validate and evaluate MAMC cut-offs for diagnosing PEW in Malaysian HD patients.

Methods: A three-phase cross-sectional study was conducted with training, validation and testing phases using a five-fold cross-validation approach against Frisancho reference. A total of 953 Malaysian HD patients were included in the analysis. Secondary

* Corresponding author. Department of Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
E-mail address: zulfitri@upm.edu.my (Z.A.M. Daud).

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data from previous Malaysian HD studies were utilized for both the training and validation phases, accounting for about 85% of the dataset. The remaining 15% of the dataset, used for the testing phase, comprised newly collected data. Data collection involved face-to-face interviews, anthropometric measurements, biochemical results, clinical data, and dietary assessments. PEW was diagnosed using the ISRNM criteria. Descriptive analysis was used to establish Malaysians HD MAMC cut-offs at P_{50} for PEW diagnosis, as per ISRNM criteria. The area under the curve (AUC) of the receiver operating characteristics curve assessed and compared the validity of these new cut-offs against the Frisancho reference.

Results: The P_{50} MAMC for Malaysian HD males was markedly lower than the Frisancho reference (24.29 cm *vs* 28.08 cm), whereas for females, it was slightly higher (23.14 cm *vs* 22.17 cm). The newly established Malaysian HD-specific MAMC cut-offs demonstrated excellent discrimination ability, outperforming Frisancho cut-offs for both validation ($AUC_{Malaysian}$ = 0.904 *vs* $AUC_{Frisancho}$ = 0.812) and evaluation ($AUC_{Malaysia}$ = 0.871 *vs* $AUC_{Frisancho}$ = 0.749).

Conclusion: These MAMC cut-offs serve as the first Malaysian HD-specific references, enhancing PEW diagnosis for clinical practice and future research.

Introduction

Hemodialysis (HD) is the primary renal replacement therapy (RRT) for patients with end-stage renal failure (ESRD), with its provision in Malaysia projected to triple by 2040. [1] A key concern is the susceptibility of HD patients to nutritional deficits is attributed to suboptimal dietary intake, with malnutrition, particularly protein energy wasting (PEW), being highly prevalent. [2] PEW is a severe condition, characterized by the decline of body protein and energy reserve, standing as a significant predictor of infections, morbidity and mortality in HD population. [3] Its prevalence is higher among HD patients compared to those on other RRTs, [4] [-7] underscoring the need for regular nutritional assessment for this patient group to prevent further complications as they greatly impact patient's quality of life and increase mortality rate. [8–11].

The International Society of Renal Nutrition and Metabolism (ISRNM) defines PEW through four key criteria: (a) body mass; (b) muscle mass; (c) serum chemistry; and (d) dietary data. [12,13] Among these, mid-arm muscle circumference (MAMC) below the 50th percentile (P_{50}) of the reference population serves as a critical ISRNM criterion under the muscle mass domain for assessing PEW. [12] Given its reliability and objectivity, MAMC acts as an essential anthropometric parameter for evaluating somatic protein reserves, serving as an early marker of nutritional decline [14] and a robust predictor of better mental health and longer survival in HD patients. [15] Despite its clinical significance, population-specific MAMC reference values tailored to the Asian population remain absent, highlighting a pressing research gap that demands urgent attention.

As a result, Malaysian healthcare systems rely on MAMC reference values derived from the Caucasian-based Frisancho reference, which is grounded in data from the National Health and Nutrition Examination Survey (NHANES) conducted in the United States, [16] [-17] for diagnosing PEW using ISRNM criteria. [12] However, these reference values do not account for the unique physiological characteristics of the Asian population. For instance, Asians tend to have higher subcutaneous fat and body fat percentages than Caucasians, which can influence MAMC measurements

by contributing to greater skinfold thickness and potentially masking true muscle mass. [18] Moreover, healthy-based reference values are not always appropriate for diagnosis in diseased population. [19,20] Consequently, reliance on these reference values risks inaccurate PEW assessment due to inherent population differences, leading to misclassification or misdiagnosis. Despite its importance, no study has developed Malaysian-specific MAMC reference values for diagnosing PEW in HD patients. Therefore, this research aimed to establish, validate and evaluate population- and gender-specific MAMC reference values at P_{50} tailored to Malaysian HD patients for accurate PEW diagnosis.

Methods

Study design and study population

This was a three-phase cross-sectional study consisting of training (Phase I), validation (Phase II) and testing (Phase III), using a robust comparative five-fold cross-validation approach against the Frisancho reference to establish, validate, and evaluate population-specific MAMC reference values for diagnosing PEW in Malaysian HD patients, as illustrated in Figure 1.

Phase I (Training Phase) - Secondary data were collected from 19 HD centers in the Klang Valley, Malaysia, including government, private and non-governmental dialysis centers. These data were sourced from the screening and baseline data from the Palm Tocotrienol in Chronic Hemodialysis (PATCH) [5,11,21,22], Ramadan [23], and Nutrition Literacy [24] studies, forming the internal dataset, which accounted for approximately 85% of the total dataset. During this phase, the internal dataset was divided into five subsets (folds) for cross-validation. In each iteration, four subsets (about 70% of the total dataset) [25] were used as the training set to compute the MAMC cut-offs at P_{50}. This process was repeated over 5 iterations, with different combinations of four subsets used as the training set in each interaction, to ensure robust and unbiased estimates. The final P_{50} MAMC cut-offs for each gender were determined by calculating the arithmetic mean of the cut-offs obtained across all iterations.

Phase II (Validation Phase) – In this phase, one subset (about 15% of the total dataset) from each iteration in the internal dataset was used as the validation set to assess the discriminative performance (internal validity) of the P_{50} MAMC cut-offs computed from the remaining four subsets (training set) in diagnosing PEW for each gender. As in the training phase, this process was repeated across all five iterations, and the final discriminative performance was calculated by averaging the results from all iterations.

Phase III (Testing Phase)- The discriminative performance of the final P_{50} MAMC cut-offs, derived from the training set, was further evaluated using external data (15% of the total dataset) collected from two additional dialysis centers not included in the training and validation phases. This external dataset was unique and non-overlapping with the earlier phases, serving as a completely independent dataset to assess the external validity of the newly established P_{50} MAMC cut-offs for the Malaysian HD population.

Selection criteria

The same selection criteria were applied across all three phases of the study. Eligible participants included Malaysian adults ($\geq$18 years) undergoing maintenance HD three times per week for a minimum of three months. Exclusion criteria included: (i) visual, hearing or speech impairment; (ii) cognitive disorders such as Alzheimer's, dementia, bipolar disorder or severe mental illness; (iii) hospitalized for more than three months (iv) acute illness (e.g., pneumonia, sepsis, acute cardiovascular events, decompensated heart failure, and COVID-19); or terminally ill; (v) recent major surgical procedures; (vii) contraindications for BIA measurements (upper or lower limb amputation, metallic implants or the presence of a pacemaker or overt signs of fluid overload such as severe edema and shortness of breath); (viii) right or left-side paralysis; (x) participation in another clinical trial, and (xi) dietary misreporting.

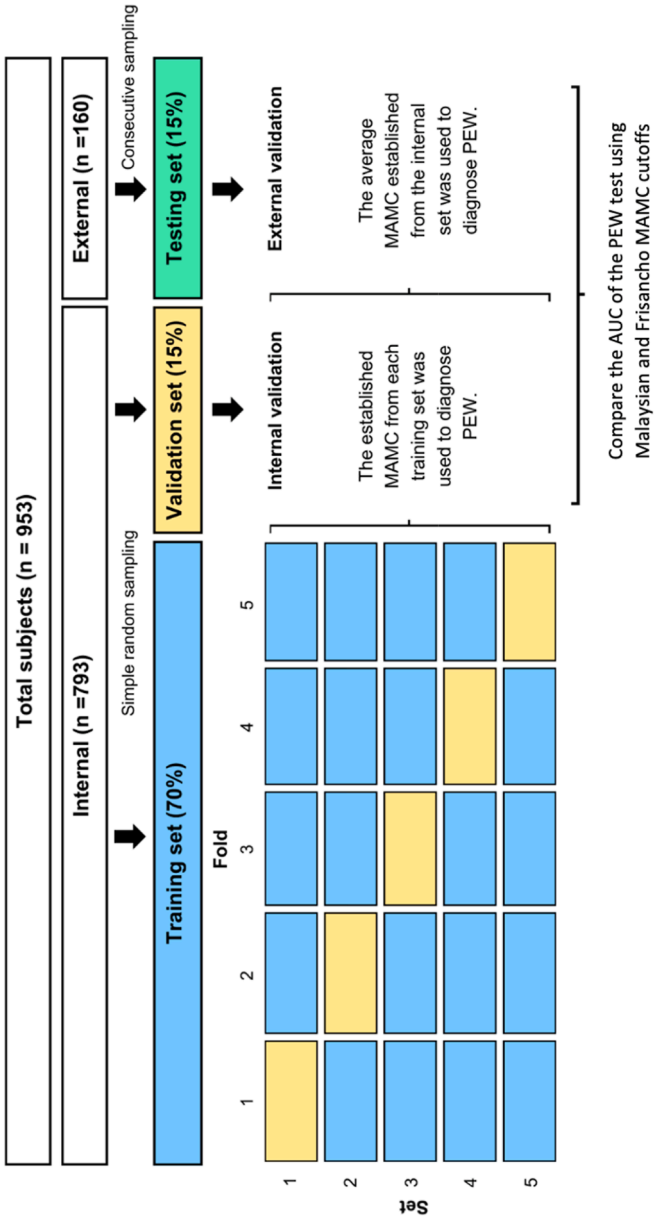

Figure 1. Five-fold cross-validation.

Data collection

Data were collected through face-to-face interviews, incorporating anthropometric measurements, biochemical data, dietary assessment and clinical data. Data collection was conducted between June 2017 and May 2024 across multiple dialysis centers in Malaysia. The privacy and confidentiality of patients were prioritized, and informed consent was obtained through signed consent forms. All research procedures adhered to established protocols from earlier studies [5,21–24] which serve as secondary data sources. Ethical approvals for all study phases were obtained from the Ethics Committee of the National Medical Research Register, Ministry of Health, Malaysia (NMRR-078-2015; NMRR-18-1514-42126; NMRR-17-2756-37435).

Sociodemographic characteristics and clinical data

Sociodemographic information, including age, gender and ethnicity, was recorded through in-person interviews. Whereas, clinical data such as dialysis vintage, dialysis adequacy (Kt/V), and the presence of comorbidities were retrieved as secondary data from the participants' medical records at the respective HD centers.

Anthropometric measurements

Anthropometric measurements were performed adhering to the methodology defined by the International Society for the Advancement of Kinanthropometry's (ISAK). [26] All researchers across study sites were trained by the principal investigator (ISAK Level 2 certified) using a standardized protocol to ensure methodological consistency and minimize inter-observer variability. Height (cm), triceps skinfold (TSF) (mm) and mid-arm circumference (MAC) (cm) were measured and recorded 30 minutes before the initiation of dialysis, during the midweek of pre-dialysis treatment. [28] The participants' dry weight and body fat percentage (BF%) were determined using a multi-frequency bioelectrical impedance analysis (MF-BIA) (Fresenius BCM) [27] as recommended by KDOQI Clinical Practice Guideline for Nutrition in CKD 2020. [28] The participants' height was measured with a portable stadiometer (SECA-127, Hamburg, Germany). BMI was calculated by dividing dry weight (kg) by height (m^2).

MAC measurements were taken on the non-fistula arm, with the arm relaxed and hanging freely during the measurement, to avoid interference from arteriovenous access. A Lufkin W606PM measuring tape [29] was used to measure MAC at the midpoint between the spine of the acromion (scapula) and the tip of the olecranon (elbow). A cross mark (+) was made at the midpoint, and the circumference was measured and recorded. [30] TSF thickness was measured using a Harpenden skinfold caliper at approximately 2.0 cm above the cross mark. [31] A skinfold of subcutaneous adipose tissue was gripped with the thumb and index finger, and the caliper was released to maintain the skinfold's maximum tension. The measurement was taken after three seconds to the nearest 0.1 mm. [32] Each measurement was taken twice, and the average value was recorded. A third measurement was conducted if the difference between the first and second measurements exceeded 1% for height and MAC or 5% for TSF. [26] MAMC was determined for both genders with the equation below: [17,32,33].

$$\text{MAMC (cm)} = \text{MAC (cm)} - (\pi \text{ x TSF (cm)})$$

Serum chemistry

Serum albumin and serum cholesterol levels were extracted from the most recent medical records of the participants, as these parameters were routinely measured as part of the standard dialysis care. These parameters were used to diagnose PEW as per the ISRNM criteria for the serum chemistry domain.

Dietary intake

A 24-hour dietary record of participants was collected over three days, comprising two weekdays and one weekend, covering both dialysis and non-dialysis treatment days. [28] Dietary data were analysed using the Nutritionist Pro™ software, referencing food entries from the Malaysian Food Composition Database (MYFCD) [34] and Energy and Nutrient Composition of Food, Singapore. [35] To evaluate dietary misreporting, the ratio of reported energy intake (EI) to basal metabolic rate (BMR) was calculated, with BMR estimated using the Harris-Benedict equation. [36,37] A ratio of EI: BMR <0.8 was classified as under-reported, while a ratio >2.0 was classified as over-reported. [37,38] These thresholds were selected to reflect plausible energy intake, considering the typically sedentary physical activity levels of HD patients. Dietary records exhibiting extreme misreporting beyond these thresholds were excluded from the data analysis. Daily energy intake (DEI) and daily protein intake (DPI) were calculated based on the current body weight, except for overweight, obese and underweight participants, for whom ideal body weight was used.

Protein energy wasting status according to the ISRNM criteria

The ISRNM criteria were used in this study as they represent the only formal consensus-based CKD-specific framework for diagnosing PEW, and include MAMC as a core component, aligning directly with the study's objective. Unlike broader tools such as the Global Leadership Initiative on Malnutrition (GLIM) criteria, which remain under-evaluated in dialysis populations [39] and do not include MAMC as a key diagnostic component. PEW status was diagnosed when a patient met at least three out of four ISRNM criteria [12] with at least one component fulfilled from each criterion. The four criteria included: (i) body mass (BMI < 23.0 kg/m^2 or BF% < 10%); (ii) muscle mass (reduction of MAMC > 10% compared to the P_{50} of the reference population); (iii) serum chemistry (serum albumin < 38 g/L or serum cholesterol <2.59 mmol/L); and (iv) dietary intake (DEI <25 kcal/kg/day or DPI <0.80 g/kg/day).

Statistical analyses

Descriptive analysis

Univariate analysis was performed to describe the characteristics of the participants. Categorical variables were summarized as frequencies (percentages), while continuous variables were presented as means ± standard deviations for normally distributed data or as the median (interquartile range, IQR) if skewed.

Five-fold cross-validation

A *k*-fold cross-validation framework was employed to establish, validate and rigorously evaluate the P_{50} MAMC cut-off values tailored for the Malaysian HD population. A five-fold cross-validation was chosen in this study as it represents a standard practice in statistical modeling, stroking an optimal balance between computational efficiency and reliable performance estimation. [40] Its appropriateness for this study was further justified by the study's sample size, ensuring that each fold retained sufficient statistical power to facilitate robust validation and testing, as determined using MedCalc for Windows, version 19.4 (MedCal Software, Ostend, Belgium) for receiver operating characteristic (ROC) curve analysis (≥75 subjects per gender).

In line with the standard practice in model development and cross-validation, the total dataset was first stratified by gender and divided into the following datasets:

- Internal development and validation set (85%): This subset comprised of participants recruited from 19 dialysis centers. A five-fold cross-validation procedure was conducted within this set. Specifically, the data were randomly partitioned into 5 equal subsets (folds) using a stratified random sampling approach within each gender implemented in R version 4.4.2 to ensure balanced representation and avoid gender-related bias across folds. In each interaction, 4 folds (~70% of the

total sample) were designated as the training set to establish the MAMC cut-off values, while the remaining subset (~15% of the total sample) was used for internal validation to assess the internal validity of the newly established Malaysian MAMC reference for PEW diagnosis. This iterative process was executed across all 5 folds to fortify the robustness of the MAMC cut-offs derivation and minimize potential biases, ensuring the reliability of the final estimates. To ensure reproducibility, random sampling was performed using fixed seed prior to fold assignment.

- Testing or external validation set (15%): This subset consisted of a fully independent sample of participants recruited from two additional dialysis centers. It was not used in model training or internal validation and served exclusively to assess the generalizability and diagnostic performance (external validity) of the newly established Malaysian HD-specific MAMC cutoffs in separate HD settings.

The use of a 70:15:15 split for training, internal validation, and external testing is consistent with established practices in statistical modeling and machine learning and was further guided by sample size requirements for reliable ROC analysis. This approach ensures both internal robustness and real-world applicability of the proposed cut-offs.

To further assess the discriminative performance of the newly established Malaysian HD-specific MAMC cut-off values in diagnosing PEW using ISRNM criteria, the Frisancho reference [17] was included as a comparative standard. Frisancho reference was chosen over an existing Asian MAMC reference from Japan [41] because it is endorsed by the Malaysian Medical Nutrition Guidelines for CKD [16], making it more relevant to local clinical practice where population-specific benchmarks remain unavailable.

In the training phase, descriptive statistics (i.e., frequencies) were used to compute the Malaysians HD-specific P_{50} MAMC cut-off values for each gender. In the validation and testing phases, the discriminate performance of the newly established MAMC cut-off values, as well as the Frisancho reference, was assessed and compared using the area under the curve (AUC) of the ROC curve analysis. A higher AUC value suggests a greater diagnostic test accuracy of the established MAMC cut-off. An AUC value of 0.5 is considered a chance level, indicating no discrimination ability. [42] AUC values between 0.7 and 0.8 are regarded as acceptable; between 0.8 and 0.9 are considered excellent; and scores greater than 0.9 are considered perfect. [43] Statistical analyses were conducted using IBM SPSS version 29 for the training phase and "pROC" package in R version 4.4.2 for the validation and testing phases, based on completed case analysis (missing data <5%).

Results

Patients characteristics

A total of 1,010 HD patients were recruited for this study across three phases, as illustrated in Figure 2. However, only about 953 patients (94.4%) were included in the final analysis after excluding dietary mis-reporters (n=31) and those with missing values (n=26). The dataset was split into 70% for training (n=633), 15% for validation (n=160), and 15% for testing (n=160).

Participant characteristics are presented in Table 1. Gender distribution was balanced at a 1:1 ratio for both the internal and external sets. The internal set (n = 793) comprised 50.4% male (n=400) and 49.6% female (n=393), whilst the external set (n=160) carried 47.5% male (n=76) and 52.5% female (n=84) proportions. The median age of the internal set was higher than the external set (57.0 years *vs* 52.0 years) but proportionately shared a similar ethnic profile.

PEW parameters across internal and external participants

The comparisons of PEW parameters across groups are presented in Table 2. BMI differences were significantly lower for the external set than the internal set (23.85 ± 4.43 kg/m^2 <25.48 ± 5.01 kg/m^2, P <0.001). Approximately 30% of participants in both sets fell below the ISRNM diagnostic threshold

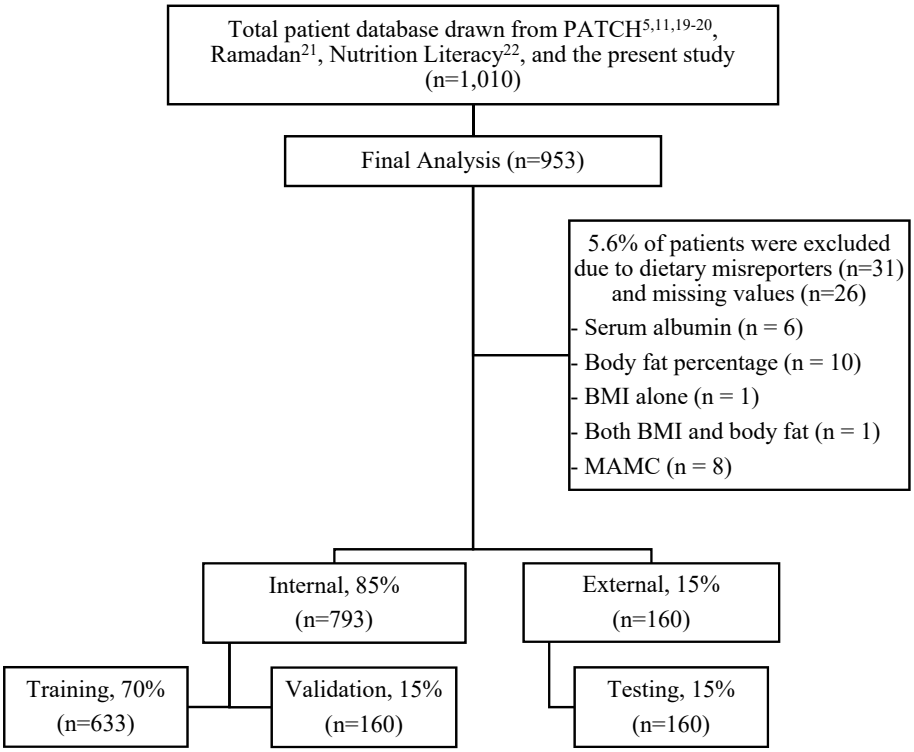

Figure 2. Patient Recruitment.

for BMI (<23.0 kg/m^2). Notably, only a negligible proportion of patients had a body fat percentage below 10.0% with either the internal set (0.1%; 1/793) or and the external set (0.6%; 1/160).

The overall mean MAMC for the internal set was significantly higher than the external set values (23.84 ± 3.23 cm vs 23.24 ± 3.13 cm, *P*=0.032), with men showing higher values compared to women (24.06 ± 3.09 vs 23.43 ± 3.32 cm, *P*=0.002). In contrast, MAC measurements were not differentiated by gender (internal set, male: 29.78 ± 4.32 cm and female: 29.62 ± 4.41 cm, *P*=0.610; external set, male: 28.89 ± 4.04 cm and female: 28.47 ± 4.34 cm, *P*=0.529). But significantly more fat stores were indicated for female than male as per TSF measurements (internal set, female: 19.18 ± 8.33 mm and male: 18.01 ± 8.21 mm, *P*=0.046: external set, female: 18.28 ± 7.36 mm and male: 16.02 ± 6.61 mm, *P*=0.044).

Serum albumin levels for the external set were lower than the internal set (37.13 ± 4.43 g/L< 41.0 ± 3.58 g/L, *P*<0.001) with a higher proportion in the external set (58.1%) had serum albumin <38.0 g/L compared to the internal set (21.1%). Females had lower albumin levels than males across both sets (internal set, female: 40.79 ± 3.60 g/L and male: 41.20 ± 3.54 g/L, *P*=0.121: external set, female: 36.41 ± 4.10 g/L and male: 37.92 ± 4.46 g/L, *P*=0.028). Serum cholesterol levels were similar across both sets (*P*=0.213) although females had higher serum cholesterol levels than males in both sets (*P*>0.05 for both).

The overall DEI (25.16 ± 7.27 vs 22.34 ± 7.21 kcal/kg/day, *P*<0.001) and DPI (0.95 ± 0.32 vs 0.81 ± 0.32 g/kg/day, *P*<0.001) were significantly higher for the external set than the internal set. Despite this, more than half of patients in both sets failed to meet the minimum recommended daily energy intake of 25 kcal/kg/day and protein intake of 0.8 g/kg/day (67.5% and 51.8% respectively).

Table 1
Patients characteristics

Variables	Overall		Male		Female	
	Internal (n = 793)	External (n = 160)	Internal (n = 400)	External (n = 76)	Internal (n = 393)	External (n = 84)
Age (years)[a]	57.0 (48.0–64.0)	52.0 (40.0–62.3)	56.5 (47.0–64.0)	52.0 (38.5–61.3)	58.0 (49.0–64.0)	53.0 (40.8–62.3)
18–24	13 (1.6)	9 (5.6)	7 (1.8)	7 (9.2)	6 (1.5)	2 (2.4)
25–34	53 (6.7)	22 (13.8)	29 (7.2)	9 (11.8)	24 (6.1)	13 (15.5)
35–44	88 (11.1)	20 (12.5)	47 (11.8)	9 (11.8)	41 (10.4)	11 (13.1)
45–54	172 (21.7)	47 (29.4)	89 (22.3)	22 (28.9)	83 (21.1)	25 (29.8)
55–64	275 (34.7)	28 (17.5)	133 (33.3)	14 (18.4)	142 (36.1)	14 (16.7)
≥ 65	192 (24.2)	34 (21.3)	95 (23.8)	15 (19.7)	97 (24.7)	19 (22.6)
Ethnicity, n (%)						
Malay	357 (45.0)	88 (55.0)	183 (45.8)	43 (56.6)	174 (44.3)	45 (53.6)
Chinese	242 (30.5)	47 (29.4)	113 (28.2)	18 (23.7)	129 (32.8)	39 (34.5)
Indian	188 (23.7)	23 (14.4)	99 (24.8)	14 (18.4)	89 (22.6)	9 (10.7)
Others	6 (0.8)	2 (1.3)	5 (1.3)	1 (1.3)	1 (0.3)	1 (1.2)
Dialysis vintage (months)[a]	74.9 ± 62.3 (3–420)	78.9 ± 65.3 (4–420)	74.8 ± 63.8 (4–420)	77.1 ± 63.5 (9–420)	75.1 ± 60.8 (3–312)	80.7 ± 67.2 (4–361)
Comorbidities, n (%)						
Hypertension	618 (78.8)	137 (85.6)	300 (76.1)	62 (81.6)	318 (81.5)	75 (89.3)
Diabetes mellitus	326 (41.6)	48 (30.0)	164 (41.6)	24 (31.6)	162 (41.5)	24 (28.6)
Hyperlipidemia	186 (23.7)	37 (23.3)	99 (25.1)	10 (13.3)	87 (22.3)	27 (32.1)
CVD	83 (10.6)	39 (24.4)	46 (11.7)	15 (19.7)	37 (9.5)	24 (28.6)
Others[b]	151 (19.2)	27 (16.9)	75 (19.0)	12 (15.8)	76 (19.5)	15 (17.9)
No. of comorbidities, n (%)						
None	81 (10.3)	10 (6.3)	46 (11.6)	6 (7.9)	35 (9.0)	4 (4.8)
One	264 (33.6)	56 (35.0)	129 (32.7)	31 (40.8)	135 (34.6)	25 (29.8)
Two	264 (33.6)	56 (35.0)	130 (32.9)	24 (31.6)	134 (34.4)	32 (38.1)
≥ Three	176 (22.4)	38 (23.7)	90 (22.8)	15 (19.8)	86 (22.0)	23 (27.5)
Dialysis adequacy (Kt/v)	1.62 ± 3.59 (0.60–4.33)	1.60 ± 0.40 (0.79–3.61)	1.59 ± 0.44 (0.61–4.33)	1.47 ± 0.39 (0.79–3.61)	1.65 ± 0.34 (0.60–3.10)	1.71 ± 0.37 (1.08–2.94)
< 1.2	78 (12.0)	16 (10.1)	54 (16.8)	12 (16.0)	25 (7.6)	4 (4.8)
≥ 1.2	570 (88.0)	142 (89.9)	267 (83.2)	63 (84.0)	302 (92.4)	79 (95.2)
Overhydration (L)	1.9 ± 1.5 (-2.3-8.5)	1.8 ± 1.7 (-3.2-6.6)	1.9 ± 1.5 (-2.3-8.5)	2.0 ± 1.7 (-0.9-6.6)	2.0 ± 1.5 (-1.3-8,5)	1.6 ± 1.6 (-3.2-6.6)

[a] Age presented as median (Q1-Q3) as skewed distributions; Categorical data presented as frequency (percentage).

MAMC cut-off values

The training, validation and testing results of the P_{50} Malaysian HD-specific MAMC cut-off values for the overall population (n = 953), as well as for male (n = 476), and female (n = 477) participants, are summarized in Table 3.

Overall participants

For all 953 participants (internal, n = 793; external, n = 160) with combined data for males and females, the newly established Malaysian MAMC cut-off values consistently outperformed the Frisancho reference for the AUC values for PEW diagnosis across all validation sets, as shown in Table 3 (Fold 1 = 0.869 *vs* 0.785; Fold 2 = 0.865 *vs* 0.792; Fold 3 = 0.938 *vs* 0.883; Fold 4 = 0.925 *vs* 0.820; Fold 5 = 0.903 *vs* 0.787). Among these, significant differences were observed in Fold 4 (P=0.023) and Fold 5 (P=0.019). Overall, the AUC value using the Malaysian MAMC cut-off values was significantly higher than Frisancho reference (0.904 *vs* 0.812, P<0.001).

Similarly, in the testing set, the AUC results using the established Malaysian MAMC cut-offs ($MAMC_{male}$: 24.29 cm; $MAMC_{female}$: 23.14 cm) were significantly higher than those obtained with the Frisancho reference ($AUC_{Malaysian}$: 0.871 *vs* $AUC_{Frisancho}$: 0.749, P = 0.022). These findings demonstrate that the newly established Malaysian HD-specific MAMC cut-off values not only exhibited excellent diagnostic test accuracy but also consistently outperformed the Frisancho reference for PEW diagnosis in Malaysian HD patients.

Table 2
Comparisons of protein energy wasting criteria across internal and external participants

Variables[a]	Overall				Male				Female			
	Total (n=953)	Internal (n = 793)	External (n = 160)	*P*-value	Total (n=476)	Internal (n = 400)	External (n = 76)	*P*-value	Total (n=477)	Internal (n = 393)	External (n = 84)	*P*-value
BMI (kg/m^2)	25.21 ± 4.95 (13.20–56.50)	25.48 ± 5.01 (13.20–56.50)	23.85 ± 4.43 (15.10–36.30)	<0.001[b]	25.21 ± 5.03 (15.1–56.50)	25.54 ± 5.10 (15.5–56.5)	23.46 ± 4.26 (15.1–34.9)	<0.001[b]	25.21 ± 4.88 (13.2–55.3)	25.43 ± 4.92 (13.2–55.30)	24.20 ± 4.57 (15.2–36.30)	0.035[b]
< 18.5	63 (6.6)	45 (5.7)	18 (11.3)		34 (7.1)	23 (5.8)	11 (14.5)		29 (6.1)	22 (5.6)	7 (8.3)	
< 23.0	254 (26.7)	208 (26.2)	46 (28.7)		122 (25.6)	101 (25.3)	21 (27.6)		132 (27.7)	107 (27.2)	25 (29.8)	
≥ 23.0	636 (66.7)	540 (68.1)	96 (60.0)		320 (67.2)	276 (69.0)	44 (57.9)		316 (66.2)	264 (67.2)	52 (61.9)	
MAMC (cm)	23.74 ± 3.22 (14.1–36.1)	23.84 ± 3.23 (14.1–36.1)	23.24 ± 3.13 (15.8–32.5)	0.032[b]	24.06 ± 3.09 (15.7–36.1)	24.11 ± 3.12 (15.7–36.1)	23.84 ± 4.04 (17.7–31.0)	0.492	23.43 ± 3.32 (14.1–33.3)	23.58 ± 3.32 (14.1–33.3)	22.71 ± 3.23 (15.8–32.5)	0.029*
MAMA (cm^2)	37.30 ± 12.18 (9.3–93.9)	37.77 ± 12.31 (9.3–93.9)	35.31 ± 11.33 (13.4–77.7)	0.023*	37.90 ± 12.35 (9.6–93.9)	38.21 ± 12.53 (9.6–93.9)	36.22 ± 11.26 (15.0–66.5)	0.196	36.71 ± 11.99 (9.3–81.6)	37.18 ± 12.07 (9.3–81.6)	34.50 ± 3.23 (15.8–32.5)	0.062
MAC (cm)	29.53 ± 4.35 (16.2–48.5)	29.70 ± 4.36 (16.2–48.5)	28.67 ± 4.19 (17.5–40.5)	0.006*	29.64 ± 4.28 (18.0–48.5)	29.78 ± 4.32 (18.0–48.5)	28.89 ± 4.04 (19.8–40.5)	0.097	29.42 ± 4.42 (16.2–46.8)	29.62 ± 4.41 (16.2–46.8)	28.47 ± 4.34 (17.5–39.0)	0.030*
TSF (mm)	18.36 ± 8.11 (4.0–48.2)	18.59 ± 8.29 (4.0–48.2)	17.21 ± 7.08 (5.2–39.2)	0.030*	17.69 ± 8.0 (4.0–45.6)	18.01 ± 8.21 (4.0–45.6)	16.02 ± 6.61 (6.4–37.0)	0.023*	19.02 ± 8.17 (4.5–48.2)	19.18 ± 8.33 (4.5–48.2)	18.28 ± 7.36 (5.2–39.2)	0.359
Body fat (%)	28.92 ± 8.17 (5.2–58.6)	28.74 ± 7.87 (5.2–58.6)	29.8 ± 9.62 (9.1–51.7)	0.187	27.42 ± 7.15 (5.2–56.9)	27.35 ± 6.74 (5.2–56.5)	27.79 ± 9.03 (9.1–50.2)	0.689	30.42 ± 8.83 (13.9–58.6)	30.16 ± 8.64 (14.3–58.6)	31.63 ± 9.62 (13.9–51.7)	0.198
< 10.0	2 (0.2)	1 (0.1)	1 (0.6)		2 (4.0%)	1 (0.3)	1 (1.3)		0	0	0	
> 10.0	951 (99.8)	792 (99.9)	159 (99.4)		474 (88.6)	399 (99.8)	75 (98.7)		477 (100.0)	393 (100.0)	84 (100.0)	
Serum albumin (g/L)	40.34 ± 3.98 (24.0–52.0)	41.0 ± 3.58 (24.0–52.0)	37.13 ± 4.43 (26.0–48.6)	<0.001*	40.66 ± 3.89 (24.0–49.0)	41.20 ± 3.54 (24.0–49.0)	37.92 ± 4.46 (27.0–48.6)	<0.001*	40.02 ± 4.05 (26.0–52.0)	40.79 ± 3.60 (29.8–52.0)	36.41 ± 4.10 (26.0–45.0)	<0.001*
< 38.0	260 (27.3)	167 (21.1)	93 (58.1)		110 (23.1)	72 (18.0)	39 (51.3)		150 (31.4)	96 (24.4)	54 (64.3)	
≥ 38.0	693 (72.7)	626 (78.9)	67 (41.9)		366 (76.9)	328 (82.0)	37 (48.7)		327 (68.6)	297 (75.6)	30 (35.7)	
Serum cholesterol (mmol/L)	4.35 ± 1.01 (1.70–10.20)	4.33 ± 0.99 (1.94–8.00)	4.44 ± 1.10 (1.70–10.20)	0.213	4.31 ± 1.06 (1.70–10.20)	4.30 ± 1.01 (2.06–8.00)	4.35 ± 1.28 (1.70–10.20)	0.731	4.40 ± 0.96 (1.94–7.70)	4.37 ± 0.96 (1.94–7.70)	4.54 ± 0.96 (2.55–6.87)	0.152
< 2.59	23 (2.4)	18 (2.3)	5 (3.4)		15 (3.2)	11 (2.8)	4 (5.6)		8 (1.7)	7 (1.8)	1 (1.2)	
≥ 2.59	919 (97.6)	775 (97.7)	144 (96.6)		457 (96.0)	389 (97.3)	68 (94.4)		462 (98.3)	386 (98.2)	76 (90.5)	
Daily energy intake (kcal/kg/day)	22.81 ± 7.30 (5.97–55.46)	22.34 ± 7.21 (5.97–55.46)	25.16 ± 7.27 (6.30–49.24)	<0.001*	22.88 ± 7.37 (6.30–55.46)	22.53 ± 7.34 (7.75–55.46)	24.71 ± 7.25 (6.30–49.24)	0.018*	22.75 ± 7.24 (5.97–52.68)	22.15 ± 7.09 (5.97–52.68)	25.56 ± 7.30 (11.63–48.67)	<0.001*
< 25	643 (67.5)	552 (69.6)	91 (56.9)		317 (66.6)	271 (67.8)	46 (60.5)		326 (68.3)	281 (71.5)	45 (53.6)	
≥ 25	310 (32.5)	241 (30.4)	69 (43.1)		159 (33.4)	129 (32.3)	30 (39.5)		151 (31.7)	112 (28.5)	39 (46.4)	
Daily protein intake (g/kg/day)	0.83 ± 0.32 (0.14–2.15)	0.81 ± 0.32 (0.16–2.15)	0.95 ± 0.32 (0.14–2.11)	<0.001*	0.84 ± 0.31 (0.14–2.15)	0.82 ± 0.32 (0.25–2.15)	0.92 ± 0.31 (0.14–2.02)	0.012*	0.83 ± 0.33 (0.16–2.11)	0.80 ± 0.32 (0.16–2.10)	0.97 ± 0.34 (0.31–2.11)	<0.001*
< 0.8	494 (51.8)	450 (56.7)	44 (27.5)		248 (52.1)	223 (55.8)	25 (32.9)		246 (51.6)	227 (57.8)	19 (22.6)	
≥ 0.8	459 (48.2)	343 (43.3)	116 (72.5)		228 (47.9)	177 (44.3)	51 (67.1)		231 (48.4)	166 (42.2)	65 (77.4)	

[a] Continuous data presented as mean ± standard deviation (range), data analyzed using independent *t* test; Categorical data presented as frequency (percentage).
[b] Significant improve the discrimination power; BMI, body mass index; TSF, triceps skinfold; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; MAMA, mid-arm muscle area.

Table 3
Five-fold cross-validation for the P_{50} malaysian HD-specific MAMC cut-off values

Set	Variables	Subset	n	Malaysian reference					Frisancho reference					
				MAMC 50th percentile (cm)	PEW, n (%)	AUC	Sensitivity (%)	Specificity (%)	MAMC 50th percentile (cm)	PEW, n (%)	AUC	Sensitivity (%)	Specificity (%)	*P*-value
Internal	Male	1	80	24.30	7 (8.8)	0.934	100	49.3	28.08	15 (18.8)	0.803	100	12.3	0.024[a]
		2	80	24.26	6 (7.5)	0.860	100	54.1		11 (13.8)	0.752	100	13.0	0.107
		3	80	24.32	15 (18.8)	0.934	100	52.3		19 (23.8)	0.880	100	8.2	0.239
		4	80	24.36	11 (13.8)	0.958	100	52.2		22 (27.5)	0.843	100	10.3	0.026[a]
		5	80	24.24	9 (11.3)	0.880	88.9	50.7		25 (31.3)	0.821	100	7.3	0.426
		Total	400	24.29	48 (12.0)	0.917	97.9	52.3		92 (23.0)	0.815	100	10.4	<0.001[a]
	Female	1	79	23.13	11 (13.9)	0.818	90.9	66.2	22.17	8 (10.1)	0.805	75.0	69.0	0.918
		2	79	23.14	8 (10.1)	0.857	75.0	62.0		8 (10.1)	0.857	75.0	78.9	1
		3	79	23.13	6 (7.6)	0.967	100	57.5		5 (6.3)	0.981	100	79.7	0.582
		4	78	23.15	11 (14.1)	0.915	90.9	61.2		9 (11.5)	0.914	88.9	72.5	0.992
		5	78	23.17	11 (14.1)	0.934	100	59.7		8 (10.3)	0.959	100	68.6	0.540
		Total	393	23.14	47 (12.0)	0.901	91.5	61.3		38 (9.7)	0.902	86.8	74.1	0.984
	Overall	1	159		18 (11.3)	0.869				23 (14.5)	0.785			0.200
		2	159		14 (8.8)	0.865				19 (11.9)	0.792			0.239
		3	159		21 (13.2)	0.938				24 (15.1)	0.883			0.149
		4	158		22 (13.9)	0.925				31 (19.6)	0.820			0.023[a]
		5	158		20 (12.7)	0.903				33 (20.9)	0.787			0.019[a]
		Total	793		95 (12.0)	0.904				130 (16.4)	0.812			<0.001[a]
External	Male	1	76	24.29	16 (21.1)	0.855	93.8	55.0	28.08	31 (40.8)	0.738	100	11.1	0.141
	Female	1	84	23.14	16 (19.0)	0.916	100	58.8	22.17	15 (17.9)	0.914	100	66.7	0.967
	Overall	1	160		32 (20.0)	0.871				46 (28.9)	0.749			0.022[a]

[a] Significant improve the discrimination power; MAMC, mid-arm muscle circumference; PEW, protein energy wasting; AUC, area under the curve.

Male

The P_{50} MAMC values derived from the five-fold internal subsets (n=400) were as follows: Fold 1 (24.30 cm), Fold 2 (24.26 cm), Fold 3 (24.32 cm), Fold 4 (24.36 cm) and Fold 5 (24.24 cm), with an average of 24.29 cm. These reference values consistently outperformed the Frisancho cut-off in term of diagnostic test accuracy for PEW diagnosis across all validation sets, as shown in Table 3. For instance, the Malaysian MAMC demonstrated superior AUC values compared to across all folds: Fold 1 (0.934 *vs* 0.803), Fold 2 (0.860 *vs* 0.752), Fold 3 (0.934 *vs* 0.880), Fold 4 (0.958 *vs* 0.843), Fold 5 (0.880 *vs* 0.821), with an average AUC of 0.917 *vs* 0.815 ($P<0.001$). Significant differences were observed in Fold 1 ($P=0.024$) and Fold 4 ($P=0.026$).

Similar results were observed in the external set (n=76), where the Malaysian MAMC cut-off (24.29 cm) continued to outperform the reference ($AUC_{Malaysian}$: 0.855 *vs* $AUC_{Frisancho}$: 0.738, $P=0.141$). Although the difference was not statistically significant, the improvement in AUC reflects a qualitative enhancement in diagnostic test accuracy from acceptable to excellent discrimination ability, further confirming the robustness of the Malaysian MAMC reference for PEW diagnosis.

Female

A total of 477 female participants were included in the analysis, with 393 in the internal set and 84 in the external set. The P_{50} MAMC cut-off values for Malaysian HD females were as follows: Fold 1 (23.13 cm), Fold 2 (23.14 cm), Fold 3 (23.13 cm), Fold 4 (23.15 cm), and Fold 5 (23.17 cm), yielding an average of 23.14 cm, which was slightly lower than the average for Malaysian HD males ($P=0.002$).

The AUC values for PEW diagnosis using the Malaysian MAMC reference ($AUCs_{Malaysian}$: Fold 1 = 0.818; Fold 2 = 0.857; Fold 3 = 0.967; Fold 4 = 0.915; Fold 5 = 0.934; Average = 0.901) were generally comparable (with all P values >0.05) to those using the Frisancho MAMC reference ($AUCs_{Frisancho}$: Fold 1 = 0.805; Fold 2 = 0.857; Fold 3 = 0.981; Fold 4 = 0.914; Fold 5 = 0.959; Average = 0.902), both demonstrating excellent to almost perfect discriminative ability. In the testing set, the Malaysian MAMC cut-offs continued to demonstrate robust performance, achieving an AUC value of 0.916. Similarly, the Frisancho reference for females achieved an AUC of 0.914, with no significant difference between them ($P = 0.967$).

Discussion

This pioneering study is the first to establish and validate gender-specific MAMC references tailored specifically for PEW diagnosis in Malaysian HD patients. While these cut-offs are intended for use within the Malaysian HD population, there may also be applicable to other Southeast Asian countries such as Singapore, Brunei and Indonesia, where population-specific MAMC references remain unavailable, given the similarities in ethnic and demographic profiles. However, further validation studies are needed to confirm their validity in these regions. Notably, when compared with the Japanese MAMC reference (P50) for HD patients (Male: 24.29cm [Malaysia] *vs* 23.67cm [Japan]; Female: 23.14cm [Malaysia] *vs* 20.25cm [Japan]), substantial differences were observed (Table 4). These findings highlight the broader need for population-specific MAMC cut-offs across Asian HD populations. By addressing the distinct body composition and dietary intake characteristics of Malaysian HD patients, this study enhances the diagnostic precision of PEW assessments and provides a vital foundation for region-specific diagnostic criteria in Asia. This situation mirrors the case of BMI

Table 4
Comparative table for the MAMC reference across populations

Gender	Mid-arm Muscle Circumference (MAMC) at 50th percentile (cm)		
	Malaysia[a]	Frisancho[b]	Japanese[c]
Male	24.29	28.08	23.67
Female	23.14	22.17	20.25

[a] The average of MAMC at 50th Percentile for Malaysian HD Patients derived from the present study's participants.
[b] The average of MAMC at 50th Percentile using Frisancho reference (U.S. healthy population) [17].
[c] The average of MAMC at 50th Percentile using Japanese reference (Japanese HD population) [39].

where Asian-specific cut-offs are required for a general population instead of using global standards, as Asians tend to have higher body fat percentages at lower BMI. [44–46] The robustness of these findings is supported by the inclusion of large and representative samples of Malaysian HD patients, with equal gender distribution and a diverse ethnic composition reflective of the Malaysian population. The generalizability of our findings is further supported by the comparable sociodemographic distribution of study participants with the Malaysian Dialysis and Transplant Registry 2022 report [47] and the difference between PEW parameters for internal and external sets, indicating that our sample could be a good representation of the broader Malaysian HD population, which serves as a good reference.

Significant differences between the MAMC references highlight the limitations of relying on the Frisancho cut-offs for PEW diagnosis in Malaysian HD patients. The Frisancho cut-offs, which are derived primarily from a Caucasian-based population, may not adequately account for the physiological and demographic differences in body composition between populations [48], leading to inaccurate PEW diagnosis. For instance, using the Malaysian MAMC cut-offs, the prevalence of PEW for male HD patients was 13.4%, whereas applying the Frisancho cut-offs would have resulted in a higher prevalence of 25.8%. While the numerical difference in PEW prevalence may seem marginal, its clinical implications can be profound. Overestimation of PEW cases could lead to unnecessary interventions, inefficient resource allocation, and compromise patient care. Moreover, it could intensify the burden on the dialysis care system, which is already constrained by manpower shortage. Furthermore, based on the ISRNM criteria, PEW can be diagnosed if the MAMC value falls $\geq$10% below the population's reference (P50). In our study, the calculated 10% reduction from the Malaysian MAMC P50 yielded thresholds of 21.86 cm for males and 20.83 cm for females, which closely matched the optimal MAMC cut-off values derived from our further sensitivity analysis using ROC for predicting PEW diagnosis: 22.35cm for males (sensitivity: 92.2%; specificity: 83.7%) and 20.85cm for females (sensitivity:88.9%; specificity: 87.7%). This alignment further validates the appropriateness of our newly established P50-derived references and supports the internal consistency of our diagnostic framework. Accurate diagnosis is also pivotal for biomarker discovery and validation, as misclassification could dilute research findings and hinder the development of targeted therapies for HD patients. [49].

As expected, the newly established Malaysian MAMC cut-off for male HD patients (24.29 cm) was notably lower than the mean Frisancho MAMC (28.08 cm). This difference underscores the distinct physiological and pathophysiological profiles of Malaysian HD patients compared to Caucasians, who generally present with greater muscle mass due to differences in genetics, diet, and physical activity patterns. [50] This finding challenges the assumption that global cut-offs can be universally applied, highlighting the risk of misdiagnosis and inappropriate clinical decisions when population-specific characteristics are not considered.

Surprisingly, the established Malaysian MAMC cut-off for female HD patients (23.14 cm) was slightly higher than the mean Frisancho MAMC (22.17 cm), contradicting the trend observed in male HD patients. The discrepancy may be attributed to the higher level of subcutaneous fat and adiposity typically seen in Asians, particularly females. [51] Older females exhibit greater variability in subcutaneous fat distribution, with adipose tissues often being uneven, heterogeneous and flabby. [52] Paradoxically, while higher subcutaneous fat is supposed to increase the TSF values, which would lower the calculated MAMC [17,32,33], the larger MAMC value observed in Malaysian HD females may result from the disproportionate larger MAC driven by subcutaneous fat deposition in the upper arms. The formula for calculating MAMC only adjusts for fat at the triceps site through TSF and does not account for residual fat distribution in other regions of the arm (e.g., bicep). This limitation of the formula allows some residual fat to remain unadjusted, contributing to an inflated MAMC value. Furthermore, the challenges of using skinfold caliper to measure thick or even fat layer may also lead to underestimated TSF values, compounding the issue. [28,53,54] These factors could explain why Malaysian HD females exhibit higher MAMC cut-offs compared to the Frisancho reference, despite potentially lower lean muscle mass. For example, the PEW prevalence of Malaysian HD females using the Malaysian cut-off was 13.2%, whereas a lower PEW prevalence (11.1%) was found when applying the Frisancho reference. Despite this, it did not have much impact on the diagnostic test accuracy and

the resultant PEW prevalence in female HD participants, reaffirming the robustness and clinical utility of the newly established Malaysian MAMC cut-off for females.

This study identified several limitations that warrant consideration in future research. Firstly, anthropometric and body composition measurements were conducted before dialysis, deviating from the recommended post-dialysis timeframe to avoid fluid redistribution. [55] However, this decision was rooted in ethical considerations, acknowledging the vulnerabilities of HD patients post-dialysis (e.g., fatigue, irritation, bleeding risk). We addressed these challenges by strategically conducting the measurements during the midweek of the pre-dialysis treatment to balance between ethical imperatives and methodological rigor. Another limitation lies in the variability of blood analysis techniques across the study sites, which may have impacted the comparability of biochemical results retrieved from patient medical records. However, this variability also reflects the real-world clinical settings, where PEW diagnosis relies on routinely collected biochemical results. Additionally, using MAMC in ROC analysis for PEW diagnosis may raise concerns about the "independent" assumption in ROC analysis, as it is also a criterion for PEW diagnosis. However, our objective was to compare two cut-offs rather than evaluate MAMC as independent predictor of PEW. This approach is common in diagnostic research, including studies on metabolic syndrome [56] and sarcopenia [57,58], where cut-offs are evaluated despite overlap with diagnostic criteria. Moreover, since the ISRNM criteria remain the only available established framework for PEW, incorporating MAMC in validation is necessary and inevitable. Although no patients were excluded for acute illness in the present study, we acknowledge that this pre-specified criterion may limit the generalizability of the cut-offs to more clinically unstable populations. Future studies should consider validating the proposed MAMC thresholds in acutely ill dialysis patients to assess their applicability in higher-risk populations. Lastly, a key limitation of this study is the absence of age-specific MAMC cut-offs, as MAMC values vary with age. [28].

However, due to sample size constraints, age-stratified references cannot be reliably developed validated and tested. Despite this, our gender-specific cut-offs outperformed the age- and gender-specific Frisancho reference, demonstrating superior classification accuracy in Malaysian HD patients. Importantly, gender-specific but age-neutral MAMC cut-offs from the present study may offer a more practical and simplified reference for clinical implementation. Future studies with larger cohorts should build upon this work to develop age-specific MAMC references, further improving its diagnostic precision.

A potential concern of this study is that our MAMC cut-offs were derived from HD patients rather than healthy, well-nourished population, unlike others anthropometric references such as the Frisancho standards (NHANES) or the Japanese 2001 reference. This is because applying healthy-based references to HD patients may overestimate PEW prevalence, as dialysis patients inherently have lower muscle mass. This approach is consistent with practice in laboratory medicine and clinical nutrition, where clinically meaningful cut-offs are often established from diseased populations, such as diagnostic thresholds for diabetes or disease-specific growth charts for children with Down syndrome and cerebral palsy. Likewise, ISRNM threshold for BMI and serum albumin are also lower than those typically used for healthy population, reflecting disease physiology. Notably, in our sensitivity analysis (data not shown), ISRNM's P50-10% values were 21.86 cm for males and 20.83 cm for females, closely aligning with the empirically derived ROC/Youden optimal cut-offs in our cohort (22.35cm for male; 20.85cm for female), further supporting internal validity. Nonetheless, future work incorporating healthy Malaysian cohorts would allow benchmarking against normative data and enhance cross-population comparability.

Practical application

The study findings carry profound practical implication for advancing the clinical and nutritional managements of HD patients in Malaysia and other Southeast Asian regions with similar demographic characteristics. By establishing population-specific MAMC cut-offs, this research provides that enhance the accuracy of PEW diagnosis. It also addresses the critical limitations of relying on Western-derived reference, ensuring that diagnostic criteria are both culturally and regionally relevant. Beyond clinical setting, the adoption of the newly established MAMC cut-offs could also improve research validity by reducing misclassification bias and fostering more reliable biomarker discovery.

Lastly, this study sets a precedent for addressing the unique needs of diverse patient populations, underscoring the importance of regional adaptations in global healthcare practices.

Conclusion

In conclusion, this study established the first gender-specific MAMC reference values at P_{50} tailored for diagnosing PEW in Malaysian HD patients. These HD-specific references demonstrated superior diagnostic accuracy compared to the widely used Frisancho standards, supporting their clinical utility in local dialysis settings. However, they should not be interpreted as normative cut-offs for the general Malaysian population, as they were derived from a patient cohort with inherently reduced muscle mass. Future research incorporating healthy Malaysian cohorts and other Southeast Asian populations will strengthen cross-population comparability and facilitate regional harmonization of PEW assessment in HD settings.

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Ethical approval (removed from the manuscript for blinding review)

Ethical approvals for all study phases were obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-078-2015; NMRR-18-1514-42126; NMRR-17-2756-37435). The PATCH study was also registered at ClinicalTrials.gov (Identifier: NCT02913690).

Authors' contribution

Z.A.M.D. and J-.H.L. designed the research. Q-.Q.H., J-.H.L., N.I.H.A., B-.H.K., and S.S. contributed to the data collection. Q-.Q.H., J-.H.L., N.I.H.A., B-.H.K., and S.S. formed the data consolidation and data entry. Q-.Q.H., and J-.H.L. analyzed the data and performed statistical analysis. Q-.Q.H., and J-.H.L. wrote the manuscript. T.K., ZAMD, P.K., N.I.H.A., L-.F.T., B-.H.K., and S.S. critically reviewed and revised the manuscript. All authors read and approved the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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